CHAPTER 4

EFFECTS OF SPIRAPRIL AND CAPTOPRIL ON REGIONAL BLOOD FLOW IN CHRONIC CONGESTIVE HEART FAILURE; A COMPARISON BETWEEN A SHORT- AND LONG-ACTING ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

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Summary

Spirapril is a new angiotensin-converting enzyme (ACE) inhibitor with a long duration of action. To determine whether the duration of inhibition of serum ACE activity may affect regional blood flow, we compared spirapril with captopril, an ACE inhibitor with a short duration of action. Both the short- and long-term effects were studied in patients with mild to moderate congestive heart failure. Calf, renal, and hepatic blood flow measurements were performed in the morning, before intake of the study medication; 24 hours after the previous dose of spirapril (n=9 patients) and 12 hours after the previous dose of captopril (n=9 patients). Serum ACE activity after 1, 6, and 12 weeks was significantly reduced in the patients receiving spirapril, but not in those receiving captopril. The decrease in mean arterial pressure was more pronounced in the spirapril group. Calf blood flow showed a small, but not significant increase in both the spirapril and captopril treated patients. Effective renal blood flow increased significantly only in the patients treated with spirapril. Although filtration fraction showed a tendency to decrease in the spirapril group, this decrease was only significant in the captopril group. No changes were observed in hepatic blood flow. Cerebral blood flow measurements were performed after intake of the first dose of study medication and after 12 weeks, immediately after drug intake. Although mean arterial pressure was significantly reduced in the two treatment groups both after the first dose and after 12 weeks, this did not affect cerebral blood flow. In conclusion, despite a significantly prolonged decrease in mean arterial pressure and serum ACE activity in the spirapril treated patients, no marked differences in regional blood flow between the two ACE inhibitors were observed.

Introduction

In the pathophysiology of chronic congestive heart failure (CHF), redistribution of regional blood flow plays an important role [1]. The renin-angiotensin system and the sympathetic nervous system are major neurohumoral compensatory mechanisms involved in the derangements of peripheral circulation in CHF [2]. The activation of these systems does not cause a uniform vasoconstrictor effect across the vascular beds. Blood flow is reduced to the cutaneous, renal, and splanchnic vascular beds in an effort to preserve flow to the coronary and cerebral circulations [3,4].

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve exercise performance, patient well-being, and survival in the management of patients with CHF [5-8]. ACE inhibitors may affect regional blood flow by inhibition of the formation of angiotensin II. Although ACE inhibitors are similar in their

mechanism of action, differences in their pharmacokinetics and pharmacodynamics, may influence their clinical use in various populations of CHF patients [9]. For instance, the risk for prolonged symptomatic hypotension, compromising regional blood flow and organ function, may be greater for long-acting ACE inhibitors than for short-acting agents [5].

Spirapril is a new non-sulphydryl angiotensin-converting enzyme inhibitor with a long duration of action [10]. To determine if prolonged inhibition of serum ACE activity by spirapril may affect regional blood flow, we compared spirapril with captopril, an ACE inhibitor with a short duration of action. Both the short- and long-term effects on limb, renal, cerebral, and hepatic flow were studied in patients with mild to moderate congestive heart failure.

Methods

Patients: Patients were eligible for the study if they met the following entry criteria: 1) a history of CHF, class II or III according to the New York Heart Association, secondary to coronary artery disease or idiopathic dilated cardiomyopathy, 2) a left ventricular ejection fraction $\leq$ 40%, and 3) a peak oxygen consumption $\leq$ 20 ml/min/kg. Patients with an acute myocardial infarction or coronary bypass surgery < 3 months prior to the study, patients with unstable angina pectoris, and those with a systolic blood pressure < 100 mmHg and/or diastolic < 60 mmHg were excluded from the study. Patients who suffered from angina pectoris, chronic obstructive pulmonary disease, claudication or any other abnormality interfering with a proper conduction of the exercise test to determine peak oxygen consumption were also excluded.

Study design: The study was a double blind, randomised, comparative study in parallel groups, with a duration of 12 weeks after a single blind placebo run-in period of 1 week (= baseline). Patients were evaluated in the screening period, the placebo period, and at the end of week 1, 3, 6, and 12. The protocol was performed conformable with the guidelines established in the Declaration of Helsinki, and approved by the ethical committee of the University Hospital Groningen. Written informed consent was obtained from each patient prior to entry into the study.

Medication: Only diuretics and/or digoxine were allowed as concomitant medication and dosages were kept constant during the study. Long-acting nitrates, calcium antagonists or other vasodilators as well as inotropic agents (except digitalis) had to be discontinued, if used, before entry in the placebo period. None of the patients had been treated with an angiotensin-converting enzyme inhibitor before. All patients were on a sodium chloride restricted diet of 3-5 gram sodium

daily. At the end of the placebo period patients received a first dose of either spirapril (3.0 mg) or captopril (6.25 mg). If the first dose was tolerated well, the patients continued with spirapril 6 mg once daily + 2 placebo's or captopril 12.5 mg three times daily. At the end of 3 and 6 weeks, doses could be doubled if no adverse effects had occurred and if the clinical response was insufficient.

Exercise testing: Exercise testing on a treadmill with respiratory gas exchange measurements was conducted as previously described [11]. It was performed during the screening period, during the placebo run-in period, and at the end of week 6 and 12. All tests were performed in the morning hours, before intake of the study medication. Peak oxygen consumption was defined as oxygen consumption (ml/min/kg) at peak exercise, calculated as the mean of values during the last minute of exercise.

Regional blood flow: *Calf blood flow:* Venous occlusion plethysmography was used for measurement of calf blood flow [12]. All measurements took place in the morning before intake of the study medication. Patients laid down on a bench in a room with a constant temperature of 22°C and the legs were placed 15 cm above heart level. A strain gauge was placed around the widest part of each calf and the occlusion cuffs were placed just above the right and left knee. Venous occlusion was achieved by inflation of the cuffs to 50 mmHg; arterial occlusion was achieved by inflation of the cuffs to 50 mmHg above systolic arm blood pressure during a period of 5 minutes. Resting calf blood flow was determined by alternate venous occlusion at intervals of 5-6 heart beats. Reactive hyperaemia was induced by a period of arterial occlusion of 5 minutes followed by rapid deflation of the cuffs; hyperaemic calf blood flow was then determined by alternate venous occlusion. Calf blood flow was calculated from the rate of the initial increase in calf circumference during venous occlusion and expressed as millimeters per 100 ml of calf tissue per minute. Vascular resistance (VR) of both calves was calculated from mean arterial blood pressure (MAP) and calf blood flow (BF): VR = MAP/BF. Calf blood flow and vascular resistance of the right and the left leg were averaged prior to statistical analysis.

To determine whether an increase in peak calf blood flow after reactive hyperaemia was related to exercise capacity, as measured by means of peak oxygen consumption, patients were divided into 2 groups based on an increase in peak VO2 of > 1.0 ml/min/kg [13]. Cardiopulmonary exercise testing to determine peak oxygen consumption was performed as previously described [14].

Renal blood flow: Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured simultaneously using ^{125}I-iothalamate and ^{131}I-hippurate, respectively, according to the method described by Donker et al [15]. All patients were studied in the morning in supine position after breakfast, and without intake of the study medication. The radiopharmaceuticals were infused at

a constant rate after a priming dose was given. To determine the activities of ^{125}I-iothalamate and ^{131}I-hippurate blood samples were drawn and urine was collected in two hours portions up to 6 hours after the sustained infusion had begun. All values for ERPF and GFR were corrected for a body surface of 1.73 m^2. Filtration fraction (FF) represents the ratio GFR/ERPF.

Cerebral blood flow: Transcranial Doppler sonography was used to measure cerebral blood flow velocity [16]. Patients laid down on a bench and systolic, diastolic, and mean blood flow velocity of the middle cerebral artery were monitored at a mean depth of 55 mm via the transtemporal approach with a 2-MHz pulsed wave transcranial Doppler apparatus. Cerebral blood flow velocity was measured before and during 4 hours after intake of the first dose of the study medication at intervals of 15 minutes. A sphygmomanometer was used to measure blood pressure at the same time intervals. According to the same protocol, measurements were repeated after 12 weeks, before and after the study medication was given in the dose used at that time.

Liver blood flow: The hepatic clearance of indocyanine green was used to determine liver blood flow [17]. Indocyanine green powder was dissolved with aquous solvent (5 mg/ml). The dosage, 0.5 mg/kg bodyweight, was rapidly injected into an arm vein, and subsequently blood samples were drawn from an indwelling venous catheter at 1.5, 3, 6, 9, 12, and 15 minutes after injection. After centrifugation, the optical density of each sample was measured, using a spectrophotometer, at 805 nm. The optical density of the patient's normal serum (the blank) and the density of a known concentration added to the normal serum were used to draw a concentration-density curve. The indocyanine green concentration of each sample was obtained from this curve, and a concentration-time curve could be constructed. The clearance of indocyanine green was calculated from this curve using a computer program (RUGFIT). Measurements were performed before intake of the morning dose at the end of the placebo run-in period and at the end of week 12.

Serum ACE activity: Blood samples to analyze serum ACE activity, were drawn from an indwelling catheter in the brachial vein after 30 minutes of supine rest at the end of the placebo run-in period, and at the end of week 1, 6 and 12. All samples were drawn in the morning, before intake of the study medication. After the blood sample was taken, it was immediately centrifuged and stored at -80°C. Established techniques were used to determine serum ACE activity [18].

Statistical analysis: Qualitive differences between the two treatment groups were compared with the chi-square statistic with Yates correction for continuity and Fisher's Exact test for small numbers. Quantitative differences were tested with analysis of variance and Student's t-test; paired for within-group differences, unpaired for between group differences. Wilcoxon signed rank test was used if a

Table 1. *Baseline characteristics of the patients in the spirapril group and captopril group who completed the study.*

	Spirapril (n = 9)	Captopril (n =9)	p-value
Sex	7 M, 2F	5 M, 4 F	ns
Etiology	8 CAD, 1 IDC	8 CAD, 1 IDC	ns
NYHA class	7 II, 2 III	7 II, 2 III	ns
Age (years)	55 ± 4	62 ± 2	ns
CTR	0.51 ± 0.05	0.51 ± 0.05	ns
LVEF (%)	30 ± 2	26 ± 3	ns
Peak VO_2	18.2 ± 0.6	16.9 ± 0.6	ns
MAP (mmHg)	96 ± 4	91 ± 2	ns

Values expressed as mean ± SEM. CAD = coronary artery disease; CTR = cardio thoracic ratio; F = female; IDC = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; M = male; MAP = mean arterial pressure; n = number of patients; NYHA = New York Heart Association; Peak VO_2 = peak oxygen consumption.

normal distribution could not be assumed. Data are expressed as mean ± standard error of the mean. Differences were considered statistically significant at the 5% level, two-sided.

Results

Patients (Table 1): A total of 20 patients with a mean age of 59 ± 3 years entered the study; 14 men and 6 females. Mean left ventricular ejection fraction was 28 ± 2 % and mean peak oxygen consumption was 17.4 ± 0.5 ml/min/kg. The cause of congestive heart failure was coronary artery disease in 18 patients and idiopathic dilated cardiomyopathy in 2. At the end of the placebo run-in period 9 patients were randomized to receive spirapril and 11 patients to receive captopril. Eighteen patients completed the study; 2 patients receiving captopril were withdrawn from the study after 3 weeks of treatment because of adverse events. The baseline characteristics of the patients in the 2 treatment groups who completed the study are summarized in table 1. At the end of the study, the average daily dose of spirapril was 9.3 mg (range 6 to 12 mg), and that of captopril was 50 mg (range 37.5 to 75 mg).

Table 4. *Transcranial Doppler flow velocity measurements of the middle cerebral artery in relation to alterations in mean arterial pressure after the first dose of study medication and after 12 weeks of treatment.*

	After first dose on day 0			*After 12 weeks of treatment*		
	baseline t = 0	T max t = 3 hrs	p-value	baseline t = 0	T max t = 2.5 hrs	p-value
Spirapril						
Mean arterial pressure (mmHg)	97 ± 6	91 ± 5	< 0.05	94 ± 6	87 ± 6	< 0.05
Systolic velocity (cm/sec)	84 ± 5	83 ± 5	ns	78 ± 6	76 ± 5	ns
Diastolic velocity (cm/sec)	38 ± 3	36 ± 3	ns	32 ± 2	33 ± 2	ns
Mean velocity (cm/sec)	56 ± 3	52 ± 3	ns	48 ± 3	49 ± 3	ns
	baseline t = 0	T max t = 2 hrs	p-value	baseline t = 0	T max t = 1 hr	p-value
Captopril						
Mean arterial pressure (mmHg)	96 ± 3	87 ± 2	< 0.01	96 ± 3	88 ± 3	< 0.05
Systolic velocity (cm/sec)	73 ± 4	71 ± 3	ns	78 ± 3	73 ± 3	ns
Diastolic velocity (cm/sec)	33 ± 2	33 ± 3	ns	35 ± 2	33 ± 2	ns
Mean velocity (cm/sec)	47 ± 3	47 ± 3	ns	49 ± 2	47 ± 2	ns

Values expressed as mean ± SEM. T max = time at which the maximal significant change in mean arterial pressure occurred.

Table 3. *Effects of spirapril and captopril on peak oxygen consumption (peak VO2) and exercise time.*

	baseline	week 6	week 12
Spirapril			
Exercise time (sec)	1117 ± 62	1117 ± 60	1109 ± 87
Peak VO_2 (ml/min/kg)	18.2 ± 0.6	17.8 ± 0.8	17.7 ± 1.2
Captopril			
Exercise time (sec)	1007 ± 34	1117 ± 48	1192 ± 60 *
Peak VO_2 (ml/min/kg)	16.9 ± 0.6	18.8 ± 0.8 *	19.2 ± 1.2

Values are expressed as mean ± SEM. * indicates $p < 0.05$ within the group compared to baseline.

Calf blood flow (Table 2): Evaluable measurements of calf blood flow could be obtained from 15 patients (7 in the spirapil group, 8 in the captopril group). Both resting calf blood flow and peak calf blood flow after reactive hyperaemia showed an increase after 12 weeks of treatment with spirapril and captopril, although these changes were not statistically significant due to great variations. Mean arterial pressure at rest decreased significantly in the spirapril group after 1 and 12 weeks of treatment. Vascular resistance at rest was significantly reduced only after 1 week of treatment when compared to baseline. In the captopril group neither mean arterial pressure nor vascular resistance changed significantly. The effects on exercise capacity of both spirapril and captopril are summarized in table 3. Only in the patients treated with captopril a significant increase in exercise capacity was observed. Peak calf blood flow after reactive hyperaemia for the total group of patients, showed a significant increase after 12 weeks of treatment in those patients in whom the increment in peak oxygen consumption was > 1.0 ml/min/kg, (see methods section) (n = 6; 4 patients in the captopril group, 2 in the spirapril group): 32 ± 3 vs 24 ± 3 ml/100 ml.min at baseline, $p < 0.05$ (Figure 1). In contrast to this increase after 12 weeks, no change was observed after 1 week of treatment: 23 ± 2 vs 24 ± 3 ml/100 ml.min at baseline. In patients with ≤ 1.0 ml/min/kg increase in peak oxygen consumption (n = 9; 4 in the captopril group, 5 in the spirapril group), there was neither a change in peak

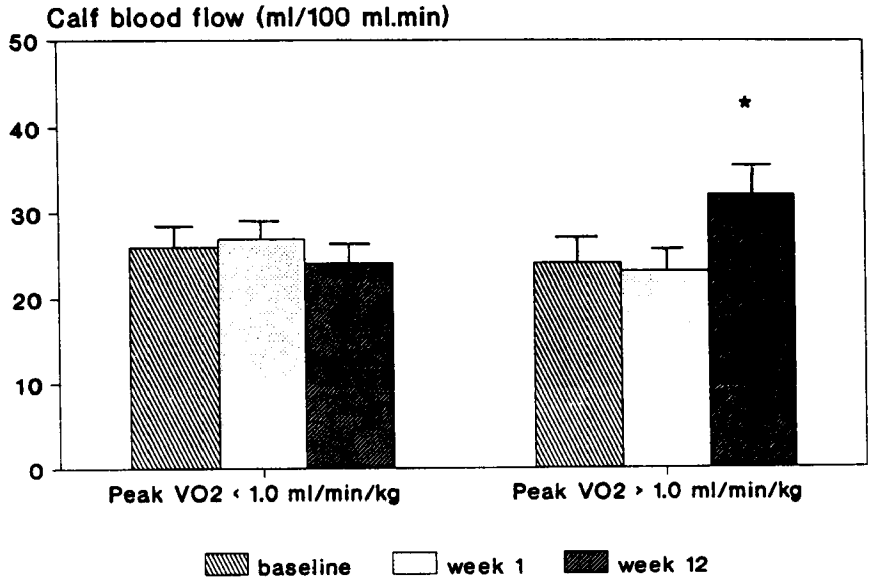

Figure 1. *Maximal calf blood flow after reactive hyperaemia in patients with > 1.0 ml/min/kg increase in peak oxygen consumption (peak VO2) vs those with < 1.0 ml/min/kg increase in peak VO2. Data expressed as mean ± SE; * indicates p < 0.05 within the group compared to baseline.*

calf blood flow after reactive hyperaemia after 1 week of treatment (27 ± 2 vs 26 ± 2 ml/100 ml.min at baseline) nor after 12 weeks of treatment (24 ± 2 ml/100 ml.min vs 26 ± 2 ml/100 ml.min at baseline).

Renal blood flow (Figure 2): There were no significant differences at baseline for ERPF, GFR, and FF between the two treatment groups. In the spirapril group, ERPF increased from 320 ± 34 ml/min/1.73 m^2 to 333 ± 38 ml/min/1.73 m^2 at the end of week 1, and to 343 ± 34 ml/min/1.73 m^2 at the end of week 12 ($p < 0.05$). GFR did not change in the spirapril group. In the captopril group, neither ERPF nor GFR showed a significant change. Although FF showed a tendency to decrease in the spirapril group both at the end of week 1 (0.27 ± 0.01 vs 0.28 ± 0.01 at baseline, $p < 0.1$) and week 12 (0.26 ± 0.01 vs 0.28 ± 0.01 at baseline, $p < 0.1$), FF decreased significantly only in the captopril group after 12 weeks (0.26 ± 0.01 vs 0.28 ± 0.01 at baseline, $p < 0.05$); FF after 1 week of treatment was 0.27 ± 0.01 in the captopril group.

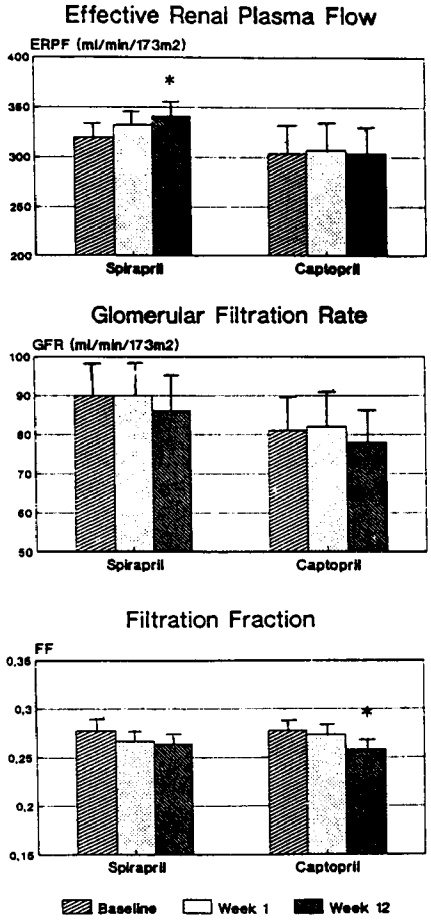

Figure 2. *Effective renal plasma flow, glomerular filtration rate, and filtration fraction at baseline, and after 1 and 12 weeks of treatment with spirapril or captopril. Data expressed as mean ± SE; * indicates p < 0.05 within the group compared to baseline.*

Cerebral blood flow (Table 4): Although mean arterial pressure showed a maximal reduction 3 hours after intake of the first dose of 3.0 mg spirapril (91 ± 5 mmHg vs 97 ± 6 mmHg, p < 0.05), transcranial Doppler waveform analysis at that time revealed no changes in systolic velocity , diastolic velocity, or mean velocity. Also in the captopril group, mean arterial pressure decreased after the first dose of 6,25 mg captopril, with a maximal change 2 hours after drug intake (87 ± 2 mmHg vs 96 ± 3 mmHg, p < 0.01). However, no changes in middle cere-

Table 2. *Calf blood flow, vascular resistance, and mean arterial pressure at baseline, after 1 week of treatment, and after 12 weeks of treatment.*

	Spirapril			*Captopril*		
	baseline	week 1	week 12	baseline	week 1	week 12
At rest:						
Mean arterial pressure (mmHg)	92 ± 4	85 ± 3 *	81 ± 4 **	91 ± 4	88 ± 3	87 ± 2
Calf blood flow (ml/100 ml.min)	3.0 ± 0.3	3.6 ± 0.8	3.5 ± 0.7	2.6 ± 0.3	2.5 ± 0.2	3.0 ± 0.4
Calf vascular resistance (mmHg.100 ml.min/ml)	35 ± 4	30 ± 4 *	36 ± 8	40 ± 3	41 ± 3	37 ± 4
Reactive hyperaemia:						
Mean arterial pressure (mmHg)	98 ± 8	93 ± 7	88 ± 4	94 ± 5	95 ± 4	92 ± 3
Maximal calf blood flow (ml/100 ml.min)	27 ± 4	25 ± 1	31 ± 5	26 ± 2	26 ± 3	28 ± 2
Calf vascular resistance (mmHg.100 ml.min/ml)	4.1 ± 0.5	3.9 ± 0.3	3.9 ± 0.9	3.9 ± 0.4	3.9 ± 0.3	3.6 ± 0.3
Half-life of hyperaemic flow (sec)	43 ± 11	38 ± 9	42 ± 10	34 ± 5	35 ± 7	41 ± 6

Values expressed as mean ± SEM; * indicates $p < 0.05$ within the group compared to baseline, ** indicates $p < 0.01$ within the group compared to baseline. There were no significant differences between the groups.

Table 5. *Hepatic blood flow as estimated from the hepatic clearance of indocyanine green (ICG) after 1 and 12 weeks of treatment.*

	baseline	week 1	week 12
Spirapril			
ICG clearance (l/min)	0.82 ± 0.15	0.84 ± 0.18	0.88 ± 0.14
Captopril			
ICG clearance (l/min)	0.64 ± 0.11	0.78 ± 0.26	0.68 ± 0.10

Values expressed as mean ± SEM. There were no significant changes between and within the 2 treatment groups.

bral artery velocity parameters were observed at that time. After 12 weeks of treatment, a maximal change in mean arterial pressure in the spirapril group was observed 2.5 hours after intake of the study medication (average dose: 9.6 mg spirapril): 87 ± 6 mmHg vs 94 ± 6 mmHg, $p < 0.05$, while in the captopril group, mean arterial pressure was maximal reduced 1 hour after drug intake (average dose: 16.7 mg captopril): 88 ± 3 mmHg vs 96 ± 3 mmHg, $p < 0.05$. However, again middle cerebral artery velocity parameters did neither change in the spirapril group, nor in the captopril group.

Liver blood flow (Table 5): Neither spirapril nor captopril caused a significant change in hepatic blood flow as estimated from the hepatic clearance of indocyanine green after 1 week and 12 weeks of treatment.

Serum ACE activity (Figure 3): In the spirapril group, serum ACE activity decreased significantly from 31 ± 5 U/l at baseline to 9 ± 3 U/l at the end of week 1 ($p < 0.01$), to 9 ± 2 U/l ($p < 0.001$) at the end of week 6, and to 13 ± 3 ($p < 0.01$) at the end of week 12. In the captopril group there was no change at the end of week 1 (25 ± 3 U/l) when compared to the end of the placebo period (27 ± 2 U/l). However, there was an increase in serum ACE activity at the end of week 6 and week 12: from 27 ± 2 U/l to 39 ± 3 U/l ($p < 0.01$) and 36 ± 2 U/l ($p < 0.01$), respectively. Serum ACE activity was different between the two treatment groups at the end of week 1, 6, and week 12 ($p < 0.0001$).

Adverse events: In the spirapril group, 1 patient experienced temporary loss of appetite. In the captopril group, 2 patients were withdrawn at the end of week 3: 1 patients because of increasing complaints of dizziness, 1 patient because of abdo-

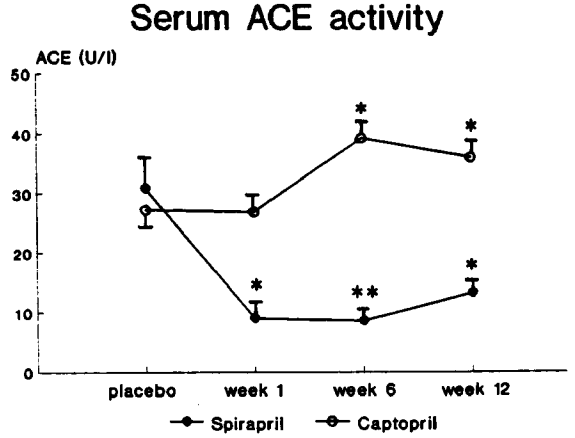

Figure 3. *Serum angiotensin-converting enzyme (ACE) activity during treatment with either spirapril or captopril; values are expressed as mean ± SE; * indicates p < 0.01 within the group compared to baseline, ** indicates p < 0.001 within the group compared to placebo run-in period.*

minal pain. Furthermore, 1 patient in the captopril group developed a stomatitis, and 1 patient a psoriatiform skin lesion. Both patients completed the study, and the complaints disappeared after the study medication was stopped at 12 weeks. No serious adverse events occurred.

Discussion

The purpose of our study was to compare the effects of the long-acting ACE inhibitor spirapril and the short-acting ACE inhibitor captopril on regional blood flow both after short- and long-term treatment in patients with mild to moderate CHF. Most of the data available in the literature with regard to regional blood flow in CHF are related to first dose administration. Our study is one of the first that has investigated both acute and long-term flow effects in a number of regions. All examinations were performed in the morning, approximately 24 hours after the previously ingested dose of spirapril, and approximately 12 hours after the previously ingested dose of captopril. This study design was deliberately chosen to determine whether the prolonged inhibition of serum ACE activity of spirapril had either beneficial or deleterious effects on limb, renal, cerebral, and hepatic blood flow compared to the usually short-lived inhibition of serum ACE activity of

captopril. Indeed, a significant decrease in serum ACE activity was observed in the patients receiving spirapril even 24 hours after drug intake at the end of weeks 1, 6, and 12. In contrast, serum ACE activity was not reduced in the patients receiving captopril; in fact serum ACE activity was slightly, but significantly higher after 6 and 12 weeks of treatment when compared to baseline values.

Despite this significant difference between the two treatment groups with regard to inhibition of serum ACE activity, calf blood flow during treatment did not significantly change, although the effect of spirapril on mean arterial pressure and vascular resistance was more pronounced. This lack on effect on resting and peak calf blood flow might have been due to the large variations. When patients were subdivided based on the increase in peak VO_2, irrespective of the ACE inhibitor they used, peak calf blood flow after reactive hyperaemia was significantly increased after 12 weeks of treatment in the patients who showed an increase of more than 1.0 ml/min/kg. In accordance with the findings of others, the increase in peak VO_2 after long-term treatment with ACE inhibitors is apparently associated with an increase in peripheral vasodilatory response [13,19]. In contrast to the effect of long-term treatment with ACE inhibitors, it has been shown that acute ACE inhibition does not alter limb blood flow [19,20]. Our study confirms these findings, as after 1 week of treatment no effect on maximal calf blood flow was observed in the group of patients with an increase in peak VO_2. These results may explain why a maximal effect of ACE inhibitors only occurs after a delayed period of time [21].

Some investigators have reported that ACE inhibition improves renal function in patients with CHF, whereas others have reported that renal deterioration is a frequent complication of treatment with ACE inhibitors [22-24]. It has been suggested that long-acting ACE inhibitors are associated with a higher risk of renal impairment because of the sustained and complete inhibition of angiotensin II formation [5]. The prolonged reduction in renal perfusion, coupled with the selective vasodilating effect of ACE inhibitors on the efferent arteriole of the glomerulus, leads to a decrease in glomerular filtration rate. However, these effects appear of less clinical consequence when dose is carefully titrated. In our study, glomerular filtration rate only showed an insignificant decrease both after captopril and spirapril. Effective renal blood flow increased significantly during treatment in the spirapril group. As the blood pressure also fell during treatment in these patients, this rise in effective renal blood flow indicates a decrease in renal vascular resistance.

Although the arterial pressure decreased significantly both after administration of the first dose of spirapril and captopril, as well as after 12 weeks of treatment, no changes in Doppler flow velocity measurements of the middle cerebral artery were observed, indicating that the cerebral blood flow was well preserved during

treatment with both ACE inhibitors. These findings are in accordance with the results of other investigators [25,26]. This preservation of cerebral blood flow may be explained by the fact that the effect of ACE inhibition on autoregulation of cerebral blood flow results from inhibition of locally produced angiotensin II, leading to a selective dilatation of larger cerebral arteries with a compensatory constriction of the smaller cerebral arteries [27].

Hepatic blood flow as estimated from the hepatic clearance of indocyanine green after 1 and 12 weeks of treatment showed no significant changes in either the spirapril group or captopril group, despite the drop in blood pressure. This observation, in conjuction with the effects on limb, renal, and cerebral flow, indicates that a redistribution of systemic blood flow occurs after ACE inhibition in patients with CHF.

In conclusion, the significantly prolonged decrease in mean arterial pressure and serum ACE activity in the spirapril treated patients did not result in marked differences in regional blood flow, when compared to the captopril treated patients. The fact that spirapril increased ERPF significantly, without affecting hepatic, cerebral, and limb flow, supports the concept that a redistribution occurs after ACE inhibition in patients with congestive heart failure.

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